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RESEARCH ARTICLE

Sequential Therapy For *Helicobacter pylori* in Elderly Patients: Effectiveness, Safety and Predictors of Success

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Abstract: ***Background*:** Sequential therapy is one of the most common regimens for *H. pylori* eradication. The progressive ageing may lead to several problems in the management of *H. pylori*.

***Objective*:** We aimed to assess the effectiveness/safety of sequential therapy in elderly patients and evaluate possible predictive factors of failure.

***Methods*:** We retrospecively enrolled 76 patients >65 years old (elderly group) and 69 controls diagnosed of *H. pylori* by upper endoscopy/histology and a non-invasive test. Patients received 10-day sequential therapy (esomeprazole 40 mg and amoxicillin 1 g for the first 5 days followed by clarithromycin 500 mg plus tinidazole 500 mg, all b.i.d). Comparison between groups was carried out by t-test or χ^2 test where appropriate. Binomial logistic regression was used to determine factors influencing treatment failure.

***Results*:** Eradication was achieved, at Intention-To-Treat analysis, in the 78.9% and 75.4% in the elderly and control group, respectively, and, at Per-Protocol analysis, in the elderly patients in the 81.1% and in controls in the 76.5%, not statistically different. Both groups experienced a similar rate of side effects (27% vs 26.5% p = 1). At univariate analysis, treatment failure in the elderly group positively correlated with female sex (OR=22.5), side effects (OR=5.3), intestinal metaplasia (OR=6.7) and gastric atrophy (OR=6.8), while negatively with antritis (OR=0.15). However, at multivariate analysis, none of the cited variables was found statistically significant.

***Conclusion*:** Sequential therapy is safe in old patients and has satisfactory effectiveness, but an "a priori" model predicting the outcome based only on clinical data is not reliable.

Keywords: *Helicobacter pylori*, eradication, elderly, sequential therapy, metaplasia.

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram negative bacterium with pathogenic effect on human gastric mucosa. It may cause both non malignant (gastritis, peptic ulcer) and neoplastic (adenocarcinoma, lymphoma) diseases of the stomach [1, 2]. The treatment of *H. pylori* infection is based on the combination of different antibiotics. The most common first-line regimens are triple therapy, consisting of a proton pump inhibitor (PPI), amoxicillin and clarithromycin for 7 to 14 days, and sequential therapy (amoxicillin for 5 days, clarithromycin and metronidazole for the following 5 days, along with PPI) [3, 4]. Nowadays, the increasing resistance to clarithromycin has caused the decreasing effectiveness of triple therapy, whose success rate has fallen to unsatisfactory percentages of about 70% [5, 6]. Sequential therapy has been reported to maintain good effectiveness [7, 8] even in the presence of some point mutations that confer resistance to clarithromycin. Indeed, the A2143G mutation in the 23S rRNA bacterial region is associated with the highest probability of treatment failure [9-11]. Nevertheless, three point mutations (A2143G, A2142C and A2142G) are mainly related to clarithromycin resistance in Western Countries [12].

The progressive ageing of human population in Western countries is leading to several problems in the management of *H. pylori*-related gastric diseases [13]. Indeed, it is known that old age is associated with a reduction of gastric mucosal barrier due to a decrease in the mucus production, while important alterations in acid and pepsin secretion have been observed [14, 15]. Moreover, such changes, along with the high rate of comorbidities and non steroidal anti-inflammatory drugs (NSAIDs) consumption, explain the reason why peptic ulcer bleeding in elderly patients is more common and has a 100-fold increased mortality in such patients [16]. Finally, aging is associated to an enhanced risk of

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pre-malignant or neoplastic conditions of the stomach [17]. On these bases, the eradication of *H. pylori* in elderly people is fundamental in order to stop the natural history of peptic ulcer and carcinoma, thus preventing their development.

Currently, few studies have specifically analyzed the sequential therapy in geriatric patients. Zullo *et al.* [18] have shown that, in elderly subjects with peptic ulcer, sequential treatment was superior to 7-day triple therapy (success rate 94.4% vs 80% respectively), and it assured the healing of the ulcer in >93% of cases. Herein, we tested empiric sequential therapy in a group of elderly patients and, moreover, we analyzed possible predictors of failure according to demographic and histopathology features.

METHODS

Patients

This was a retrospective monocentric trial, conducted in the period January 2014-August 2015 in our Gastroenterology outpatient unit. Naïve patients aging >65 years, at their first diagnosis of *H. pylori* infection were enrolled. Patients complaining of dyspeptic symptoms underwent urea breath test (UBT) or stool antigen test (SAT) for the diagnosis of *H. pylori* infection. In case of positivity of a non invasive test, we retrospectively selected patients who underwent upper endoscopy with biopsy sampling (two samples from the antrum and two from the corpus). All patients gave a written informed consent before procedure. If histological analysis confirmed the diagnosis of *H. pylori* infection, a sequential treatment was proposed to the patients. A control group of <65 year old patients was recruited, and the diagnosis of *H. pylori* was achieved as reported above. Peptic ulcer disease (PUD) was defined as a mucosal lesion larger than 5 mm in diameter. Subjects without macroscopically identified ulcers in presence of microscopic mucosal alterations were regarded as non-ulcer dyspepsia (NUD). The presence of intestinal metaplasia and gastric atrophy was established by a trained pathologist after haematoxylin and eosin staining.

We excluded patients with chronic disorders requiring cyclic antibiotic treatments or known antibiotic allergies, liver cirrhosis and chronic kidney injury [18]. For each patient, the following data were recorded: sex, age, side effects, presence of intestinal metaplasia, atrophy, antral or pangastritis involvement, smoking habits, instruction degree, assumption of NSAIDs, presence of PUD, anemia or MALT lymphoma.

Treatment

All patients who gave written informed consent received a 10-day sequential therapy, consisting of esomeprazole 40 mg b.i.d. for 10 days associated to amoxicillin 1 g b.i.d. for the first 5 days and clarithromycin 500 mg b.i.d. plus tinidazole 500 mg b.i.d for the following 5 days. The PPI was given 30 minutes before meals, while antibiotics were administered after the meals. At the end of therapy, presence of side effects, and compliance (defined as assumption of more than the 90% of prescribed drugs) were investigated by a personal or phone interview. The eradication was checked 4 to 6 weeks after treatment completion by UBT or SAT. We chose the type of non invasive test (UBT or SAT) after the end of the treatment according to the compliance of each patient. This approach was aimed to limit follow up withdrawals (drop-out). In case of PUD, metaplasia or gastric atrophy, a further upper endoscopy with biopsy sampling was suggested 6-12 months after eradication. Patients consuming aspirin for major cardiovascular events prophylaxis did not interrupt the medication during the eradication regimen. Conversely, those who assumed NSAIDs for pain management stopped the treatment during the antibiotic course, and replaced them with paracetamol.

Statistical Analysis

The study was planned as a retrospective analysis, therefore we enrolled all patients with diagnosed H. pylori infection in the period January 2014-August 2015. Since the aim was to evaluate the effectiveness of the same treatment in two groups of patients, and not to assess a novel treatment in two homogeneous groups of subjects, it is not possible to establish the "a priori" expected difference in success rate. For this reason, we could not perform the sample size calculation.

Success rates were calculated as intention-to-treat (ITT) and per-protocol (PP) analysis. The 95% Confidence Intervals (95% CI) of eradication percentages were calculated. In univariate analysis, comparison of continuous variables was performed by Student's t-test, while comparison of categorical variables was conducted by χ^2 test, and the odd ratios (OR) and their 95% confidence intervals (95% CI) were calculated by Mantel-Haenszel method. For multivariate analysis, binomial logistic regression was used to determine which factors could have influenced success/failure of sequential treatment. Then, the binomial variable success/failure was considered as dependant variable, while all other parameters as independent ones. Variables which were statistically significant at univariate analysis were considered for multivariate analysis, and OR and 95% CI were calculated. All statistical tests were 2-tailed and performed at the 5% level of significance. The statistical analysis was performed using the software SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. The analysis was carried out only in patients who completed the study (PP analysis) in order to have reliable results about efficacy, safety and outcome predictors. Data collection, statistical analysis and results interpretation have been performed in blind by three authors (FG, GL and EI, respectively).

RESULTS

Overall, 264 patients were selected, but only 145 undergoing upper endoscopy were enrolled. Seventy-six belonged to the elderly group and 69 to the control group. Two patients in the elderly group and one in the control group were lost at the follow up, since they did not undergo outpatient visit/investigation after the end of treatment (drop-out). The sequential therapy was successful, at ITT analysis, in the 78.9% (95% CI 69.7-88.1%) and 75.4% (95% CI 65.2-85.6%) in the elderly and control group, respectively, with equivalent effectiveness ($p = 0.69$). At PP analysis, eradication was achieved in the elderly patients in the 81.1% (95%

Table 1. Comparison of demographic, clinical, endoscopic and histopathologic features of enrolled patients in the elderly and control group. Statistical analysis was performed according to the PP analysis.

	Elderly group (n = 76)	Control group (n = 69)	p value
Age (mean ± standard deviation	73.3 ± 6.3	44.9 ± 12.7	**< 0.0001**
Eradication rate at ITT	78.9% (60/76)	75.4% (52/69)	0.69
Eradication rate at PP	81.1% (60/74)	76.5% (52/68)	0.54
Sex M/F	38/36	26/42	0.13
Side effects	20 (27%)	18 (26.5%)	1
Intestinal metaplasia	18 (24.3%)	6 (8.8%)	**0.15**
Gastric atrophy	12 (16.2%)	8 (11.8%)	0.48
Antritis	62 (83.8%)	59 (86.8%)	0.65
Smokers	12 (16.2%)	22 (32.4%)	**0.03**
Low instruction level	38 (51.4%)	20 (29.4%)	**0.01**
PUD	24 (32.4%)	6 (8.8%)	**0.001**
Anemia	34 (45.9%)	6 (8.8%)	**<0.0001**
MALT lymphoma	2 (2.7%)	2 (2.9%)	1
NSAIDs	28 (37.8%)	9 (13.2%)	**0.001**
Polypharmacy	54 (71.0%)	25 (36.7%)	**<0.0001**

PUD: peptic ulcer disease; ITT: intention-to-treat; PP: per –protocol; MALT: mucosa-associated lymphoid tissue; NSAID: non-steroidal anti-inflammatory drug.

CI 72.2-90.0%) and in controls in the 76.5% (95% CI 66.4-86.6%), not statistically significant (p = 0.54). Both groups experienced a similar rate of side effects (27% vs 26.5% p = 1): the most common ones were diarrhea (8 cases in old patients and 7 in controls), headache (4 in old patients and 5 in controls) and metallic taste (6 in old people and 3 in controls), however no one interrupted the therapy, and all assumed >90% of prescribed drugs. As reported in Table **1**, old patients had a higher prevalence of intestinal metaplasia (24.3% vs 8.8%, p=0.15), PUD (32.4% vs 8.8%, p = 0.001) and anemia (45.9% vs 8.8%, p < 0.0001), consumed more NSAIDs (37.8% vs 13.2%, p = 0.001) and had a lower instruction level (51.4% vs 29.4%, p = 0.01). In the control group, smoking habits were more common (32.4% vs 16.2%, p = 0.03).

At univariate analysis, displayed in Table **2**, we found that treatment failure in the elderly group positively correlated with female sex (OR = 22.5; 95% CI 13.6-31.4; p < 0.0001), presence of side effects (OR = 5.3; 95% CI 1.6-18.3; p = 0.016), presence of intestinal metaplasia (OR = 6.7; 95% CI 1.9-23.4; p = 0.004) and gastric atrophy (OR = 6.8; 95% CI 1.7-26.1; p = 0.008). On the other hand, antritis inversely correlated with treatment failure (OR = 0.15; 95% CI 0.038-0.57; p = 0.008). However, at multivariate analysis, none of the cited variables was found statistically significant. The same analysis, performed in the control group, failed to detect statistically significant predictors of failure at both univariate and multivariate analysis.

A second upper endoscopy in patients with PUD demonstrated a complete healing in 16 out of 18 (88.8%) old patients who eradicated the bacterium, while the recovery of ulcer was observed only in one case who failed the eradication (16.6%). Complete healing of all six cases of PUD in control group was recorded. Of note, in all patients with a low grade MALT lymphoma (4 cases, two in each group) the sequential regimen was effective and cured the lymphoma. Nevertheless, in one case remission of intestinal metaplasia was observed, even in those who achieved the eradication.

DISCUSSION

Geriatric patients are often characterized by a condition of "frailty", with multiple co-morbidities, which expose the patients to a high risk of systemic complications and imply a more severe course of diseases [19]. *H. pylori*-related infection is the most important recognized risk factor for PUD and gastric cancer, and old patients carry an increased risk of both conditions, thus making compelling the need of eradication [13]. Between all first-line strategies, sequential therapy is one of the most diffuse, and it has gained increasing success for its good performance in comparison to classical 7-day triple therapy [20-23].

The first relevant finding of the present study is that, despite increasing antibiotic resistances, in an empiric context sequential therapy maintained an acceptable success rate (81.1% and 76.5% in geriatric patients and controls,

Table 2. Univariate and multivariate analysis of factors associated to failure of sequential therapy in the elderly group.

	Univariate Analysis				Multivariate Analysis	
	Success (n = 60)	Failure (n = 14)	p value	OR and 95% CI	p value	OR and 95% CI
Age	73.1 ± 6.1	74.4 ± 7.2	0.48	NE		
Female sex	22 (36.7%)	14 (100%)	<0.0001	22.5 (13.6-31.4	0.65	NE
Side effects	12 (20%)	8 (57.1%)	0.016	5.3 (1.6-18.3)	0.18	NE
Intestinal metaplasia	10 (16.7%)	8 (57.1%)	0.004	6.7 (1.9-23.4)	0.18	NE
Gastric atrophy	6 (10%)	6 (42.9%)	0.008	6.8 (1.7-26.1)	0.75	NE
Antritis	54 (90%)	8 (57.1%)	0.008	0.15 (0.038-0.57)	0.58	NE
Smokers	8 (13.3%)	4 (28.6%)	0.22	NE		
Low instruction level	28 (46.7%)	10 (71.4%)	0.14	NE		
PUD	18 (30%)	6 (42.9%)	0.36	NE		
Anemia	30 (50%)	4 (28.6%)	0.23	NE		
MALT lymphoma	2 (3.3%)	0 (0%)	1	NE		
NSAIDs	24 (40%)	4 (28.6%)	0.55	NE		
Polypharmacy	12 (85.7%)	42 (70%)	0.01	6.3 (1.3-29.8)		

OR: Odd ratio; CI: confidence interval; NE: not estimable; PUD: peptic ulcer disease MALT: mucosa-associated lymphoid tissue; NSAID: non-steroidal anti-inflammatory drug.

respectively), paralleling the eradication rates already described in literature [7, 24]. Second, sequential therapy confirmed his good safety, since side effects were few and did not lead to treatment withdrawal in any case [18, 25].

Our analysis demonstrated that elderly patients, differently from controls, seemed to have some predictive factors of therapy failure: female sex (OR=22.5), side effects (OR=5.3), intestinal metaplasia (OR=6.7) and gastric atrophy (OR=6.8). Conversely, antritis was a factor positively associated to successful eradication. This event strongly agreed with literature data, since it has been largely reported that patients with antritis have more chances to eradicate the bacterium and the disappearance of histological inflammation commonly occurs after eradication [26-28]. However, the multivariate analysis did not confirm such findings. It may be argued that all variables may co-operate with each other and cause treatment failure, as already hypothesized by De Francesco *et al.* [29]. Therefore, a predominant cause for unsuccessful eradication might not exist. Another explanation could be that patients who did not eradicate the bacterium were only 14, thus reducing the statistical power of the analysis.

Moreover, our study demonstrated that *H. pylori* eradication is able to heal peptic ulcer, with a satisfactory outcome close to 90%, and to cure low grade MALT lymphoma [17, 30, 31]. On the other hand, we did not observe the regression of intestinal metaplasia in elderly patients after eradication, confirming most of current evidences [32]. Indeed, metaplasia is a known risk factor for gastric cancer; further, old age is another predisposing factor to malignancy, and the coexistence of these two conditions must be accurately taken into account in surveillance programs [33, 34]. Therefore, on the basis of the present study, we would like to underline that an early detection of *H. pylori* in elderly patients is fundamental in order to stop the "Correa cascade" and prevent gastric cancer [35, 36]. Additionally, it is important to achieve the eradication with a combination of antibiotics with an acceptable safety, such as in sequential therapy, since in case of failure second line regimens would imply the use of antibiotics causing major side effects [37-39], particularly in elderly patients with many comorbidities. A limit of this study could be that it has been retrospectively performed. However all subjects received the same protocol and the fact that the statistical analysis was carried out by an author in blind from the author who collected the data may have reduced possible bias.

CONCLUSION

In conclusion, *H. pylori* eradication in elderly patients could be linked to histopathologic rather than demographic factors, nevertheless the results of multivariate analysis show how the interaction of such factors with other aspects, presumably microbiological, make difficult to establish an "a priori" predictive model for sequential therapy, without contemplating antibiotic resistances [40-43].

LIST OF ABBREVIATIONS

95% CI = 95% Confidence Intervals

ITT = Intention-To-Treat

MALT = Mucosa-Associated Lymphoid Tissue

NSAIDs	=	Non Steroidal Anti-Inflammatory Drugs
NUD	=	Non-Ulcer Dyspepsia
OR	=	Odd Ratio
PP	=	Per-Protocol
PPI	=	Proton Pump Inhibitor
PUD	=	Peptic Ulcer Disease
SAT	=	Stool Antigen Test
UBT	=	Urea Breath Test

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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